



# Vitamin D deficiency and atrial fibrillation: A cross sectional single center study

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## Original Article

### Abstract

**BACKGROUND:** Atrial fibrillation (AF) augments the risk of stroke by 4-5 times. Vitamin D is pivotal in numerous metabolic pathways. A handful of studies have explored the correlation between vitamin D deficiency (VDD) and AF outcomes. Hence, the authors sought to assess the relationship between VDD and AF outcomes.

**METHODS:** From December 2021 to February 2023, 190 patients with AF were incorporated into the authors' study. Given the seasonal fluctuation of vitamin D levels, these levels were examined from the start of December until the end of March.

**RESULTS:** The final analysis comprised 190 patients (55.8% male) with an average age of 46.22±15.03. Vitamin D deficiency, insufficiency, and sufficiency were noted in 77 (40.5%), 46 (24.2%), and 67 (35.3%) patients, respectively. Fatigue and syncope were significantly more prevalent in the VDD group than in other groups. Three-vessel disease was more frequent in the VDD group (p-value=0.04). Mortality was more prevalent in patients with VDD (6.31%) compared to the VDI (2.10%) and VDS (0.05%) groups (p = 0.03). Successful cardioversion was significantly more prevalent in the VDS group (p = 0.03).

**CONCLUSION:** A sufficient level of vitamin D was linked with a better response to cardioversion. However, low vitamin D levels are correlated with higher mortality in AF patients.

**Keywords:** Atrial Fibrillation; Vitamin D; Vitamin D Deficiency

*Date of submission:* 8/12/2023, *Date of acceptance:* 1/29/2024

### Introduction

Atrial fibrillation (AF), the most common arrhythmia, impacts 33 million individuals worldwide, with an all-cause mortality rate of 63.3 per 1,000 person-years<sup>1</sup>. The prevalence of AF has escalated in recent years, leading to a surge in mortality and morbidity<sup>2</sup>. Notably, AF amplifies the risk of stroke by 4-5 times<sup>3</sup>. Therefore, it is a significant rhythm disorder with a substantial impact on healthcare systems<sup>4</sup>. Aging, hypertension, valvular heart disease, congestive heart failure, coronary artery disease, and

diabetes mellitus are independent risk factors for AF<sup>5</sup>. Despite extensive research on AF, the etiology and underlying pathways remain poorly understood<sup>6</sup>. Vitamin D plays a crucial role in multiple metabolic pathways<sup>7</sup>. Vitamin D is a negative modulator of the renin-angiotensin-aldosterone system (RAAS)<sup>8</sup>. Both RAAS and inflammation play a significant role in the pathogenesis of AF<sup>9,10</sup>. A few studies have investigated the role of vitamin D deficiency (VDD) in the presentation, complications, and mortality of AF. Therefore, the authors aimed to evaluate the association between VDD and AF outcomes.

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## Methods and materials

### *Study Design and Participants*

This cross-sectional study was carried out from December 2021 to February 2023. The protocol was registered and received approval from the authors' local ethics committee (Approval ID: IR.RHC.RHEC.1401.087). All study procedures were performed in compliance with the Declaration of Helsinki. All participants gave written informed consent after the study protocol was explained to them.

All patients diagnosed with AF who were referred to the authors' outpatient department, including the arrhythmia clinic, or were admitted to the hospital, were initially evaluated. Patients with hypo- or hyperthyroidism, chronic renal failure, chronic obstructive pulmonary disorders, malignancy, acute infection, or previous gastrectomy were excluded from the study. Patients who used calcium or vitamin D supplements or any drugs that interfere with calcium metabolism were also excluded from the study. Owing to the seasonal variation of vitamin D, vitamin D levels were measured from the start of December until the end of March. The demographic, clinical, and laboratory data pertaining to the patients who ultimately participated in the study were sourced from the Iranian Registry of Atrial Fibrillation (IRAF)<sup>11</sup>.

## Definitions

### *Hypertension*

The authors assessed the diagnosis of hypertension using the American Heart Association (AHA) guideline, based on one of these three modalities: office-based, home-based, or ambulatory-based<sup>12</sup>. Additionally, patients with a history of antihypertensive medications were deemed hypertensive.

### *Dyslipidemia*

Dyslipidemia was identified when total cholesterol, low-density lipoproteins (LDL), and triglycerides were equal to or exceeded 240, 160, 200, and 100 mg/dL, respectively, and high-density lipoproteins (HDL) were less than 40 mg/dL<sup>13</sup>.

### *Diabetes*

Diabetes was diagnosed according to the 2016 Standards of Medical Care in Diabetes published by the American Diabetes Association (ADA)<sup>14</sup>.

### *Coronary Artery Disease (CAD)*

CAD and its severity were diagnosed with coronary angiography or coronary CT angiography in patients who presented with cardiac-related chest pain<sup>15</sup>. Double-vessel disease was defined as the presence of >50% lumen diameter narrowing in two of the three main epicardial vessel systems. Three-vessel disease referred to lumen narrowing of >50% in all three major epicardial artery systems or in the left anterior descending and proximal circumflex in left-dominant coronary arteries<sup>16</sup>.

### *CHA2DS2-VASc Score*

The CHA2DS2-VASc Score was computed based on: congestive heart failure (1 point), hypertension (1 point), age  $\geq$  75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular disease (1 point), age 65-74 years (1 point), and female gender (1 point)<sup>17</sup>.

### *AF*

AF was diagnosed as irregularly irregular R-R intervals without distinct repeating P waves and irregular atrial activations in a single-lead ECG tracing of  $\geq$  30 s or the entire 12-lead ECG<sup>18</sup>.

### *Chronic Kidney Disease Diagnosis*

Chronic kidney disease was diagnosed if the estimated glomerular filtration rate was less than 60 ml/min/1.73 m<sup>2</sup><sup>19</sup>.

### *VDD, Insufficiency (VDI), and Sufficiency (VDS) Definition*

VDD, VDI, and VDS were defined as serum 25-hydroxyvitamin D levels of less than 20ng/mL, between 20 and 29, and over 30 ng/mL, respectively.

### *Unsuccessful Electrical Cardioversion*

AF detection in a 12-lead ECG following right after cardioversion or within a 6-month follow-up; or (2) ECG Holter monitoring of AF lasting more than thirty seconds at the 6-month follow-up after electrical cardioversion.

### *Laboratory Tests*

Serum 25-hydroxyvitamin D levels were measured with a radioimmunoassay technique utilizing the Architect i2000 (Abbott Laboratories). The serum parathyroid hormone (PTH) concentration was

calculated with an immunoassay method (Siemens Immulite, Siemens Healthcare Diagnostics, Deerfield, IL, USA).

#### *Echocardiography Acquisition*

Skilled echocardiography fellows performed Transthoracic echocardiography using a Phillips Epiq 7c ultrasound system. Left ventricular ejection fraction (LVEF) was measured with the modified Simpson's biplane method<sup>20</sup>. Echocardiography was performed based on criteria of the American Society of Echocardiography and European Association of Echocardiography guidelines<sup>21</sup>.

#### *Statistical Analysis*

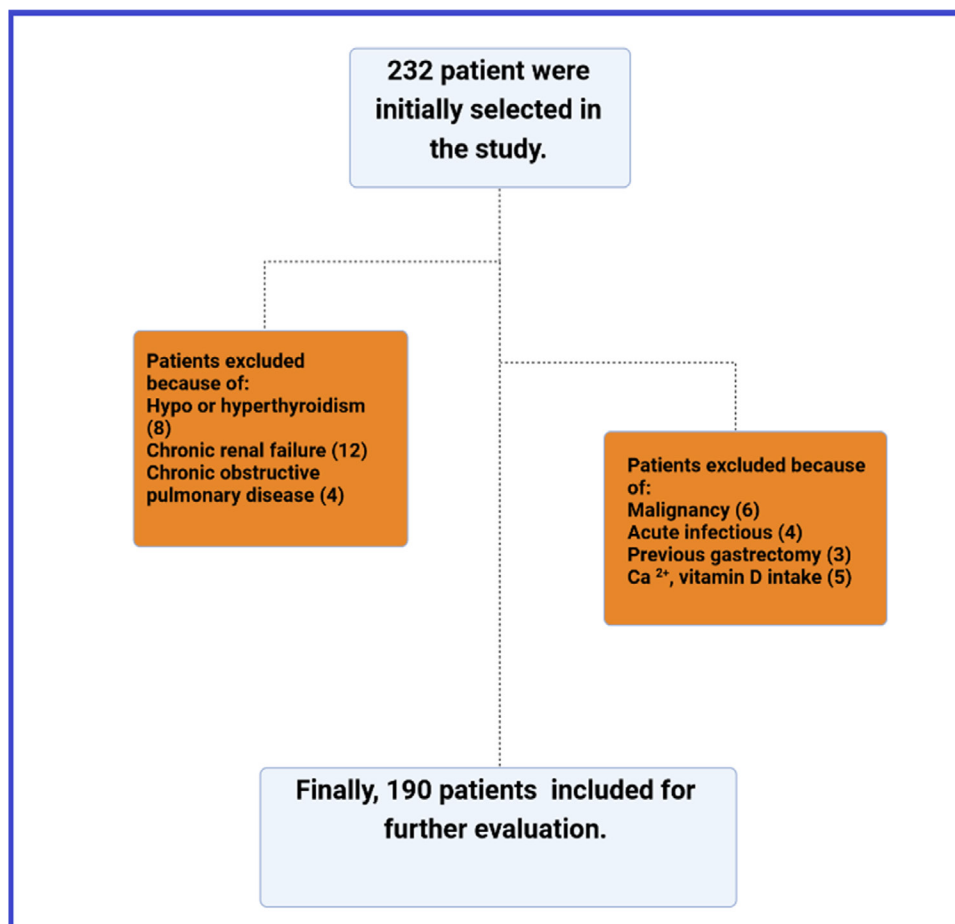
Numeric variables were expressed as mean  $\pm$  SD and categorical variables as number (%). The chi-square analysis, or Fisher exact test, assessed the significance of differences between categorical variables. Data

analysis was conducted using SPSS software, version 26. A p-value less than 0.05 was considered statistically significant.

## Results

In a study population of 190 patients, the mean age was  $46.22 \pm 15.03$  (range from 16 to 94 years). Males constituted 55.8% ( $n = 106$ ) of the study population, with the remainder being females. **Figure 1** illustrates the flowchart of the study design.

VDD, VDI, and VDS were observed in 77 (40.5%), 46 (24.2%), and 67 (35.3%) of the study population, respectively. The most prevalent symptom was palpitation, occurring in 27.36% of patients with VDD, 17.89% with VDI, and 23.1% with VDS. Fatigue and syncope were significantly more common in the VDD group than in other groups. **Table 1** presents the symptoms of the study population in different groups along with the p-values.



**Figure 1.** Flowchart of study design

Hypertension ( $p=0.03$ ) and diabetes ( $p=0.01$ ) were significantly more common in patients with VDD. Significant differences were observed in the prevalence of coronary artery disease among the VDD, VDI, and VDS groups ( $p=0.04$ ); three-vessel disease was notably more common in the VDD group. Table 2 presents the distribution of comorbidities and risk factors among the three groups of patients.

Figure 2 depicts the mortality, successful electrical cardioversion, anticoagulant therapy, and valvular heart disease based on vitamin D levels in our study population. Mortality was more common in patients

with VDD ( $n = 12$ , 6.31%) than in those with VDI ( $n = 4$ , 2.10%) and VDS ( $n = 2$ , 1.05%) groups ( $p = 0.03$ ). Prior electrical cardioversion was observed in 12 (15.58%), 5 (10.86%), and 11 (16.41%) patients from the VDD, VDI, and VDS groups, respectively, without a significant statistical difference ( $p$ -value = 0.69). The success rate of electrical cardioversion was significantly higher in the VDS group than in the VDI and VDD groups ( $p = 0.03$ ): 16.6%, 50%, and 81.8% in the VDD, VDI, and VDS groups, respectively. The need for anticoagulant therapy was significantly higher in the VDD group ( $p = 0.02$ ). \* =  $p$ -value < 0.05, SEC = successful electrical cardioversion

**Table 1.** Symptoms of the study population

Symptoms	VDD* n(%)	VDI* n(%)	VDS* n(%)	P-value
Palpitation	52(27.36%)	34(17.89%)	44(23.1%)	0.63
Dyspnea	17(8.94%)	18(9.4%)	20(10.52%)	0.12
Fatigue	15(7.89%)	13(6.84%)	3(1.57%)	0.02
Dizziness	5(2.63%)	4(2.10%)	3(1.57%)	0.66
Syncope	5(2.63%)	2(1.05%)	1(0.52%)	0.01
Anxiety	4(2.10%)	1(0.52%)	2(1.05%)	0.33
Chest pain	2(1.05%)	1(0.52%)	1(0.52%)	0.53

VDD\* = Vitamin D deficiency, VDI\* = Vitamin D insufficiency, VDS\* = Vitamin D sufficiency

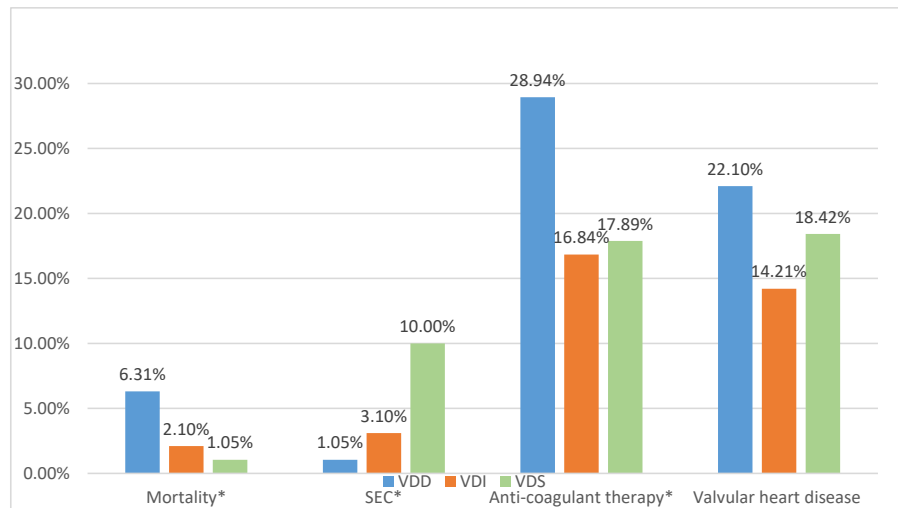
Chi square test was performed to evaluate the significant difference. P-value less than 0.05 was considered statistical significant.

**Table 2.** Comorbidities and risk factors distribution based on vitamin D

	VDD* n(%)	VDI* n(%)	VDS* n(%)	P-value	
Hypertension	44(23.15%)	20(10.52%)	24(12.63%)	0.03*	
Dyslipidemia	22(11.57%)	17(8.94%)	26(13.68%)	0.39	
Diabetes	25(13.15%)	16(8.42%)	9(4.73%)	0.01*	
Tobacco smoking	7(3.68%)	1(0.52%)	5(2.63%)	0.32	
Opium	6(3.15%)	1(0.52%)	1(0.52%)	0.12	
Coronary artery disease	Normal	52(27.36%)	35(18.42%)	61(32.10%)	0.04*
	Minimal coronary involvement	6(3.15%)	2(1.05%)	1(0.52%)	
	Two vessel disease	5(2.63%)	3(1.57%)	1(0.52%)	
	Three vessel disease	13(6.84%)	5(2.63%)	3(1.57%)	
CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	0	8	9	13	0.03*
	1	35	13	38	
	2	15	12	11	
	≥3	19	10	4	

VDD\* = Vitamin D deficiency, VDI\* = Vitamin D insufficiency, VDS\* = Vitamin D sufficiency

Chi square test was performed to evaluate the significant difference. P-value less than 0.05 was considered statistical significant.



**Figure 2.** Mortality, successful electrical cardioversion, anticoagulant therapy, and valvular heart disease population based on vitamin D level

## Discussion

VDD was observed in 40.5% of the study population. The authors noted that fatigue and syncope were significantly more prevalent in the VDD group than in other groups. Conditions such as diabetes, hypertension, three-vessel disease, and a CHA<sub>2</sub>DS<sub>2</sub>-VASc Score of  $\geq 3$  were more common in the VDD group. Furthermore, the authors found that mortality, unsuccessful electrical cardioversion, and the requirement for anticoagulant therapy were considerably higher in the VDD group.

VDD was observed in 40.5% of the study participants. This is consistent with the results of the prospective study by Qayyum et al., which analyzed vitamin D levels and found a prevalence of VDD (25-hydroxyvitamin D levels  $< 20$  ng/ml) of 42%<sup>22</sup>. In a prospective cohort study by Alonso et al., among 1866 patients who developed atrial fibrillation, 29% had a 25-hydroxyvitamin D level of less than 20 ng/ml. In the study by Ozcan et al., which compared 137 new-onset AF patients with 90 patients without AF, the rate of VDD (defined as 25-hydroxyvitamin D levels  $< 20$  ng/ml) in new-onset AF patients (VDD = 67%) was significantly higher than the control group (VDD = 51%)<sup>23</sup>. The authors suggest that these differences among this study and other rates of VDD in the literature may be due to the limited type of AF of the study population, genetics, the time of vitamin D sampling, and other factors that interfere with the serum vitamin D level. In conclusion, the

prevalence of VDD in AF patients appears to be between 30% and 40%.

In the present study, fatigue was significantly higher in the VDD group than in other groups. Beckmann et al. have reported that fatigue is associated with lower vitamin D levels<sup>24</sup>. Fatigue may present as a symptom of insufficient vitamin D levels, influencing a decrease in the optimal functioning of skeletal muscles through the modulation of vitamin D receptors<sup>25</sup>. These findings are in good agreement with the results of the authors' study.

Remarkably, syncope was more prevalent in the VDD group than in the VDI and VDS groups. Low vitamin D levels decrease serotonin production and release, decrease autonomic cardiac activity, and increase inflammation, leading to gastrointestinal dysfunction. All three mechanisms affect the brain, cardiac, and gastrointestinal autonomic systems<sup>26</sup>. VDD is associated with orthostatic hypotension in older adults<sup>27</sup>. In a study by Songül Usalp et al., VDD levels were significantly lower in patients with vasovagal syncope<sup>28</sup>. These results support the association of VDD with presenting symptoms, including fatigue and syncope. Patients with a diagnosis of AF who have the symptoms of fatigue and syncope should be evaluated for VDD.

Based on the results of this study, hypertension, diabetes, and three-vessel disease were considerably more common in the VDD group. Vitamin D deficiency plays a crucial role in hypertension through



the RAAS system<sup>29</sup>. The elimination of vitamin D receptors in recent animal studies has been linked to an increase in renin and angiotensin II levels and a decrease in endothelial nitric oxide (NO) synthase expression<sup>30</sup>. In alignment with the results of the authors' study, in a prospective cohort study of 3316 patients (1997–2000) in southwest Ludwigshafen, an increase in plasma renin and angiotensin II concentration was associated with decreased levels of 25-hydroxyvitamin D<sup>31</sup>. VDD is associated with hypertension through RAAS activation and decreased vasodilators such as NO.

In the present study, diabetes was more prevalent in the VDD group. In a systematic review and meta-analysis conducted by G. Pittas *et al.*, a significant association was seen between low vitamin D levels and the prevalence of type 2 diabetes<sup>32</sup>. (OR=0.36, 95% CI [0.16, 0.80]) In a case-control study by Targher G *et al.* performed on 390 consecutive type 2 diabetic patients and 390 non-diabetic controls, greater carotid intimal medial thickness and the prevalence of carotid atherosclerotic plaques were more prevalent in diabetic patients<sup>33</sup>. In another study, VDD prevalence (39% vs. 25%) and vitamin D levels were significantly lower in diabetic versus non-diabetic participants ( $p < 0.008$ )<sup>34</sup>. The results of our study are in good agreement with the studies mentioned above. These results suggest that VDD has a critical role in diabetes.

Atherosclerosis, a leading cause of vascular disease and a significant cause of mortality worldwide<sup>35</sup>, is notably associated with VDD. VDD plays a protective role in atherosclerosis through various mechanisms, including inhibiting platelet and leukocyte aggregation, reducing the release of pro-inflammatory cytokines, modulating the immune response, decreasing endothelial oxidative stress, and releasing vasoconstrictor metabolites<sup>36</sup>. Based on the results of the authors' study, three-vessel disease was significantly more common in the VDD group. This is consistent with a retrospective single-center study of 100 patients undergoing coronary artery bypass grafting (CABG), where two or three-vessel disease was more prevalent in patients with VDD<sup>37</sup>. Similarly, in another single-center study of 239 patients undergoing coronary angiography, severe coronary artery disease was associated with lower vitamin D levels<sup>38</sup>. Interestingly, a decrease in VDR in the left anterior descending artery of a monkey's

heart was associated with larger atherosclerotic plaques<sup>39</sup>. In conclusion, not only may VDD induce atherosclerosis, but lower levels of vitamin D are also associated with more severe coronary involvements.

Interestingly, successful electrical cardioversion was more prevalent in the VDS group than in the VDD and VDI groups. Few studies have explored the relationship between electrical cardioversion and vitamin D deficiency in patients with AF; however, some studies suggest a link between vitamin D deficiency and AF recurrence after electrical cardioversion<sup>40,41</sup>.

The authors' results are consistent with the study by Fakhry *et al.* on 200 patients with persistent AF who needed electrical cardioversion, indicating that VDD was associated with AF cardioversion failure<sup>41</sup>. Among 51 patients who underwent CV for symptomatic AF, the patients in the AF recurrence group had a lower Vitamin D level compared with the non-recurrence group ( $P = 0.001$ ; 18 ng/ml vs. 26.3 ng/ml, respectively)<sup>42</sup>. Also, vitamin D deficiency has been associated with left atrial fibrosis and an increased risk of AF recurrence after ablation<sup>43</sup>.

However, in a retrospective study analyzing 100 patients with atrial fibrillation who required cardioversion, there was no significant difference in cardioversion outcome based on VDD<sup>44</sup>. Notably, only 9% of the study population had VDD, and this low sample size may have influenced the results. In conclusion, the authors suggest that VDD may have an adverse effect on electrical cardioversion outcomes in patients with AF. Accordingly, correcting vitamin D levels is essential for AF patients, especially those with indications for electrical cardioversion.

To the authors' knowledge, this is the first report of the mortality of AF patients based on vitamin D levels. The authors found that the mortality rate of the VDD group was significantly higher than that of the other two groups. In a retrospective study of 13,331 adults older than 20 years old, it was concluded that the lowest quartile of vitamin D level ( $< 17.8$  ng/mL) is independently associated with all-cause mortality in the general population<sup>45</sup>. In a meta-analysis of prospective cohort studies, a nonlinear decrease in mortality risk was observed as circulating 25(OH) D increases within specific ranges (30–35 ng/ml). It is important to consider VDD as a risk factor for mortality in patients with AF<sup>46</sup>. Therefore, it is recommended that physicians monitor and correct

vitamin D levels in patients with AF.

According to the authors' study, AF patients with VDD significantly required more anticoagulant therapy than other groups. In a study performed on 75 patients with stable coronary artery disease, the mean platelet volume was significantly higher in patients with vitamin D levels  $< 10$  ng/mL<sup>47</sup>. Activated vitamin D upregulates antithrombotic factor (AT) and thrombomodulin gene expression and downregulates thrombogenic factor (TF) gene expression in monocyte cells<sup>48</sup>. Vitamin D is also considered one of the antioxidant agents<sup>49</sup>. In the study by Takamasa Ishii et al., genetically induced oxidative stress in mice caused thrombocytosis<sup>50</sup>. It's noteworthy that vitamin D deficiency is a risk factor for stroke<sup>51</sup>. Interestingly, a CHA2DS2-VASc Score of  $\geq 3$  was more prevalent in the VDD group than in other groups. This finding may be due to the association between VDD and diabetes, hypertension, and heart failure<sup>52</sup>. Therefore, correcting vitamin D levels in AF patients at risk of thromboembolic events<sup>53</sup> seems to be an important therapeutic option for physicians managing AF patients.

The authors acknowledge that their research may have limitations. Vitamin D levels can fluctuate depending on the time of evaluation, which could potentially impact the study results. To mitigate this limitation, the authors assessed vitamin D levels from the onset of winter until the end of March. Although this was the first study to evaluate mortality in atrial fibrillation patients with VDD, it is crucial to interpret the findings cautiously, as other factors may influence mortality in these patients.

### Conclusion

Indeed, VDD is a significant concern in patients with atrial fibrillation (AF). Symptoms such as fatigue and syncope were notably more prevalent in AF patients with VDD, underscoring the importance of monitoring vitamin D levels. Notably, VDD may not only induce atherosclerosis, but lower levels of vitamin D are also associated with more severe coronary involvements. It's crucial to consider VDD as a risk factor for mortality in patients with AF. Therefore, it's recommended that physicians monitor and correct vitamin D levels in patients with AF. While epidemiological studies have often, but not consistently, indicated that vitamin D deficiency is

a risk factor for stroke, correcting vitamin D levels in AF patients at risk of thromboembolic events appears to be a vital therapeutic option for physicians managing AF patients.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Funding

The authors would like to declare that they did not receive any financial support for this study.

### Author's Contributions

All individuals who satisfy the established criteria for authorship are acknowledged as authors, and each author affirms their substantial involvement in the research process, thereby considering a public responsibility for the content. This involvement includes contributions to the conceptualization, design, analysis, writing, and revision of the manuscript.

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**How to cite this article:** Askarinejad A, Bakhshandeh H, Heidarali M, Adimi S, Ghaemmaghani Z, Haghjoo M. **Vitamin D deficiency and atrial fibrillation: A cross sectional single center study.** *ARYA Atheroscler*. 2024; 20(1): 31-40.